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09/900,766	07/06/2001	Goran Forsberg	P02188US0 (10104199)	7699

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DUFFY, PATRICIA ANN

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1645

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/900,766	Applicant(s) Forsberg et al.
Examiner Duffy	Group Art Unit 1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE or three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- Responsive to communication(s) filed on 2-7-03.
- This action is FINAL.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- Claim(s) 1-92 is/are pending in the application.
- Of the above claim(s) 9-14, 17, 39-52, 55, 73-92 is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- Claim(s) 15, 16, 18-34, 53, 54, 56-72 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claim(s) 1-92 are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The proposed drawing correction, filed on _____ is approved disapproved.
- The drawing(s) filed on _____ is/are objected to by the Examiner.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- All Some* None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) _____.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

- Information Disclosure Statement(s), PTO-1449, Paper No(s). 4 Interview Summary, PTO-413
- Notice of Reference(s) Cited, PTO-892 Notice of Informal Patent Application, PTO-152
- Notice of Draftsperson's Patent Drawing Review, PTO-948 Other _____

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DETAILED ACTION

1. The response filed 2-7-03 has been entered into the record.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Sweden on 6-28-01. It is noted, however, that applicant has not filed a certified copy of the Swedish application as required by 35 U.S.C. 119(b).

Drawings

3. The drawings have been approved by the draftsperson.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 14 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code.

See MPEP § 608.01.

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Information Disclosure Statement

5. The information disclosure statement filed 2-7-03 has been considered. An initialed copy is enclosed.

Election/Restriction

6. Applicant's election with traverse of Group III, species SEE, 5T4 FAb fragment, lung cancer, IL-2 cytokine, Position A - 27 and Position C - 83 in Paper No. 10 is acknowledged.

7. Claims 1-14, 35-52, and 73-92 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 17 and 55 are withdrawn as being drawn to the non-elected species SEA.

Specification

8. It is specifically noted for the record that the designation in the specification "SEA/E" is used contrary to the art (Antonson et al 1997 of record). The art teaches that SEA/E is used for SAE chimerics based on the SEA sequence, whereas SEE/A is used to indicate chimerics based on the SEE sequence. Applicants specification specifically and

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deliberately renames the art described SEE/A-a, in this specification as SEA/E-18 (see page 36, Example 2, first full paragraph).

Claim Rejections - 35 U.S.C. § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 15, 16, 18-34, 53, 54 and 56-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The species of invention is drawn to products and compositions comprising the bacterial superantigen staphylococcus enterotoxin E (SEE) is conjugated to an antibody

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moiety for treatment of lung cancer wherein amino acid position 83 in region C is substituted and further comprising substitutions at amino acid position 27 in region A and position 227 in region E and further conjugation to interleukin 2. The entirety of the written description of the specification is drawn to use of the bacterial superantigen conjugates is for treatment of cancer. These claims are not enabled for the following reasons.

First, the specification fails to provide written description of the specific structure of SEE as corresponding to the functional regions A-E recited in the claims and the art does not define such. The specification lacks specific written description of the specific structural areas of SEE that define the claimed generic functional regions of regions A-E. The art does not teach these specific regions for T-cell receptor (TcR) binding and MHC class II binding for SEE, nor does the art teach the specific regions involved in MHC class II binding for SEE. While the art defines some specific residues directly involved in TcR binding of staphylococcus enterotoxin A and enterotoxin B, this specification does not teach what residues or regions are involved in TcR binding with SEE (see Antonsson et al, Journal of Immunology, page 4245, paragraph bridging columns 1-2). There is no showing in this specification that substitution of any of residues 20, 21, 24, 27, 173 and 204 affects binding to any T-cell receptor to which SEE interacts. Therefore, one

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can not make substitutions into regions that are not defined by the specification and are not defined in the art. Further, the regions "C-E" that are claimed "..to determine the binding to MHC class II molecules" are not defined in the specification as they relate to specific structural elements of SEE and these regions are not specifically defined in the art for SEE. There is no specific guidance as to how to determine the regions and how to measure binding in the regions by any assay. Therefore, one of skill in the art could not make substitutions into undefined regions in SEE. The art specifically teaches that "Although the amino acid sequences of SEA and SEE are very similar, there are differences in biological function. The V β -specificity for SEA and SEE differ (2, 17) as so their affinities to Different MHC class II alleles (9), and SEA may also have a different affinity for the TCR than SEE (16). Interestingly, in many cases chimerical molecules of SEA and SEE acquire properties that are unique and not the predicted combinations between SEA and SEE (Figs. 5-7).") Cavallin et al (The Journal of Biological Chemistry, 275(3):1665-1672, 2000; see page 1671, column 1, third full paragraph). Clearly, random substitution into undefined regions of SEE does not have a predictable outcome on the biological properties even when combined with a highly similar molecule SEA. The art specifically teaches that "..C215FAB-SEA but not C215Fab-SEE, induced T cell cytotoxicity and proliferation in these MCH class II-independent systems..." and

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"Introduction of a region from SEA, comprising amino acids 20-27, to SEE transferred the ability to engage T cells in the absence of MHC class II..." (Antonsson et al, 1997, see abstract). As such, it appears that all of amino acids 20-27 of SEA must be transferred to SEE are required to generate SADCC in any SEE mutant and the claims are not so limited. In the absence of these amino acid substitutions it is unclear as to what if any MHC class-II independent activity a chimeric SEE conjugate would possess. Absent this activity present in the superantigen, it would not be an effective T-cell targeting moiety and would not direct T cells to kill tumor cells either *in vitro* or *in vivo*. Additionally, the specification does not teach how to make and use a tripartite conjugate comprising a superantigen, antibody and interleukin. There is no teaching in this specification as filed, that such a conjugate would effectively provide for superantigen antibody dependent cellular cytotoxicity toward tumor cells. Combining a third moiety, the interleukin, provides for a bulky protein that is likely to provide steric hindrance and accessibility of the T-cell for the superantigen. It is noted that all activated T cells bind Interleukin-2. Not all T-cells bind a superantigen and different superantigens have different T cell-specificities based on the binding of the particular T cell receptor and it is not clear from the specification that combining IL-2 or any other interleukin would provide for superantigen antibody dependent killing of tumor cells *in vivo* because the IL-2 component of the conjugate would

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bind any activated T-cell and therefore misdirect the conjugate to activated T-cells rather than the antibody targeted tumor cells. The ability of the tripartite conjugate to bind activated T-cells in general via the IL-2 or tumor cells via the antibody would reasonably be expected to reduce the amount of conjugate available to attach to the tumor. As a result of the likely portioning of the tripartite conjugate between activated T cells and the tumor, one skilled in this art would have substantial reason to doubt that any tripartite conjugate would be effective to treat cancer or lung cancer in particular as is claimed. Further, it is not clear that a superantigen masked by the larger IL-2 polypeptide would be effective to mediate superantigen antibody dependent cellular cytotoxicity. As such, this specification does not teach that the presence of the IL-2 in the conjugate provides for adequate targeting of tumor cells either *in vitro* or *in vivo*. Further, SEE and variants thereof have a markedly reduced ability as compared to SEA to induce T-cell proliferation (see Cavallin et al, page 1671, column 1) and the specification does not teach that the tripartite conjugate resolves this problem. The specification is devoid of written description methodology as how to make these contemplated tri-partite conjugates in a manner that allows for superantigen antibody dependent cellular cytotoxicity for tumor cells *in vitro* or *in vivo*. Second, the art teaches that "In the context of work with fusion proteins, however, we have found that the ability for T cell MHC class II independent

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cytotoxicity, superantigen-antibody dependent cell cytotoxicity (SADCC), of SEE conjugates is poor." (Antonsson et al, U.S. Patent No. 6,514,498, column 3, lines 5-10). The art teaches that antibody conjugates with SEE have markedly decreased antibody dependent cellular cytotoxicity (see Antonsson et al, Journal of Immunology, page 4246, column 2, Figure 1) and Antonsson et al (U.S. Patent No. 6,514,498, Figure 6B). It is noted that tumor cells are allegedly killed by superantigen antibody dependent cellular cytotoxicity (SADCC) and the specification is devoid of any demonstration that the *in vitro* result correlates with efficacy of the SEE chimeric to function similarly *in vivo* to kill lung cancer cells. Furthermore, the art indicates that only SEA and SEB have been demonstrated to induce cell death *in vivo* (Weinrauch et al, Annual Review of Microbiology 53:155-87, 1999). Therefore, one of skill in the art would have reasons to doubt that the antibody conjugates based on SEE could be able to be used in any therapeutic treatment of cancer and lung cancer in particular in the absence of evidence to the contrary. This specification fails to teach the correlation of *in vitro* SADCC with therapeutically effective results in any *in vivo* model of cancer. With respect to the particular antibody 5T4, this antibody has not been apparently demonstrated to have efficacy in the treatment of lung cancer by means of this specification and one would have substantial reason to doubt that it could be used in the absence of factual evidence to the contrary.

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The entirety of the specification is drawn to use of the claimed conjugates for treatment of cancer. None of the conjugates of the invention have been demonstrated to have efficacy in any animal model of cancer and lung cancer in particular. Applicants have not demonstrated the correlation of SADCC in vitro with the 5T4- antibody conjugate with effective therapeutic function in vivo in any animal model. Although Applicant has provided a general strategy for the use of the claimed conjugates in cancer therapy, due to the unpredictable nature of the art as recited above and in antibody-mediated cancer therapeutics, the unpredictable effect of any mutation of on SDCC and SADCC in vitro, it does not appear that the general teachings for treatment of cancer are sufficient to enable the skilled artisan to make and use the claimed bipartite and tripartite conjugates as claimed for the treatment of cancer. Applicants have not provided the expected range of results, statistics or predictability of the claimed method of use of the conjugates, or the proper control conditions for the skilled artisan. Due to the high degree of unpredictability with biotechnology therapeutics and antibody-based lung cancer therapeutics in general, it is essential that Applicants' invention be demonstrated to work as claimed. In the absence of further guidance on the part of Applicants' it would require undue experimentation to make and use the conjugates as claimed for the treatment of cancer.

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12. Claims 15, 16, 18-34, 53, 54 and 56-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claims 15, 16, 18-34, 53, 54 and 56-72, the claims are *prima facie* indefinite from the use of the terminology "Region C", "Region A" and "Region E" because neither the specification or claims define these particular regions on any enterotoxin. The functional definition of Region A being a TcR binding site, regions B to E determine the binding to MHC class II molecules is not defined in either the art or this specification for any enterotoxin. These random assigned functional regions lack precision and are incomparable to the teachings of the prior art and are not structurally defined in this specification. The prior art of record fails to precisely define the TcR binding regions and MHC class II binding regions for any superantigen as recited in the claims. The metes and bounds of the claimed regions have not been set forth in the specification or in the claims such that one skilled in the art would be able to ascertain that which is included or excluded by this claim language.

With respect to claims 15, 16, 18-34, 53, 54 and 56-72, the claims are *prima facie* indefinite from the use of the terminology "low titer" because the term "low" in claim is a relative term which renders the claim indefinite. The term "low" is not defined by the

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claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

With respect to claims 19, 21, 23-25, 57, 59 and 61-63, the claims are *prima facie* indefinite in the recitation of particular residue positions in the absence of any corresponding sequence identifier. The relationship of any position in a particular sequence is relative to each and every other amino acid in the a particular sequence and the particular sequence to which the particular mutation relates is not defined by the claim. It is unclear what correspondence the referenced position has to the native molecule, if any. Correction is required.

Claim Rejections - 35 U.S.C. § 102 or 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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14. Claims 15, 16, 18, 27, 34, 53, 54, 56, 65 and 72 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Antonsson et al (WO 97/36932, published October 9, 1997).

Antonsson et al teach multiple SEE/A chimerics fused to C215FAb (C215FAb-SEE/A-A; -SEE/A-C; SEE/A-F and SEE/A-H) see page 27, Figure 6. Antonsson et al teach that the chimerics are useful for cancer therapeutics. In the absence of a structural definition of "region C" in the claims, the chimeric constructs of the art having mutations in a "C" region are deemed to structurally and therefore inherently meet the recited functionally of the claimed conjugates.

Status of Claims

15. No claims are allowed.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

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Patricia A. Duffy, Ph.D.

May 4, 2003

Patricia A. Duffy
Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600